

Initial REMS Approval: 11/2009

Most Recent Modification: 2/2011

APPENDIX A: REMICADE REMS

BLA 103772 REMICADE® (infliximab)
Tumor necrosis factor (TNF) blocker

Centocor Ortho Biotech Inc.
800 Ridgeview Drive
Horsham, PA

For further information, please call Centocor Ortho Biotech Inc.
Medical Information Department at 1-800-457-6399

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

To communicate and mitigate the risks associated with REMICADE therapy by:

- Alerting and warning healthcare providers about unrecognized histoplasmosis and other invasive fungal infections associated with Tumor Necrosis Factor (TNF) blocker use.
- Educating patients about the serious risks associated with REMICADE therapy.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each REMICADE infusion. In accordance with 21 CFR 208.24, Centocor Ortho Biotech Inc. will institute the following measures:

Infusion Centers:

- A Medication Guide is provided with each REMICADE vial. The box for each single vial also contains the following instructions: "Provide Medication Guide to Patient."
- Additional copies of the revised Medication Guides will be provided to infusion centers/sites as well as reminder to provide them to patients with each visit.
- Instructions for obtaining electronic copies of the revised Medication Guide from the website www.Remicade.com will be included.

Physician offices:

- Revised Medication Guides will be provided for distribution by prescribing (as defined in Section 2.2) physicians.

The Medication Guide is attached to this REMS.

B. Communication Plan

Centocor Ortho Biotech Inc. will implement a communication plan consisting of a Dear Healthcare Provider Letter, Dear Infusion Center Letter, and the REMICADE Serious Fungal Infection Education Guide to be disseminated to infusion centers, prescribers (ie, rheumatologists, dermatologists, and adult/pediatric gastroenterologists), pulmonologists, infectious disease specialists, and primary care physicians (ie, Family Practice, General Internists, Obstetrician/Gynecologists, and Emergency Medicine) who may potentially prescribe TNF blockers or treat patients who receive TNF blockers. The communication plan will convey the following information:

- The risk of developing invasive fungal infections, including histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections while treating with TNF blockers
- Provide descriptive information on the signs and symptoms of fungal infections, including histoplasmosis.
- Provide references and background information regarding the treatment of these infections.

These materials will also be available in printable form on a separate REMS website that can be accessed via a link (eg, “Important Safety Information Regarding Serious Infections including TB and Fungal Infections”) from the company website within 60 days of the REMS approval.

A mass mailing of educational materials including the professional labeling, the Dear Healthcare Provider Letter, the REMICADE Serious Fungal Infection Education Guide, and the Medication Guide will be sent to all prescribers (as defined above), Pulmonary and Infectious Disease specialists, and Primary Care physicians (as defined above) within 60 days of REMS approval.

A mass mailing of educational materials including the professional labeling, the Dear Infusion Center Letter, the REMICADE Serious Fungal Infection Guide, and the Medication Guide will be sent to directors (or responsible heads) of infusion centers within 60 days of REMS approval. The letter will indicate to infusion centers that the revised Medication Guide is to be provided and reviewed with patients with each REMICADE infusion. Also, instructions for obtaining electronic copies of the revised Medication Guide from the website www.Remicade.com will be included.

The Dear Healthcare Provider Letter, Dear Infusion Center Letter, and the Remicade (infliximab) Serious Fungal Infections Education Guide are appended to this REMS.

C. Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use

D. Implementation System

An implementation system is not a required component of the REMS because there are no elements to assure safe use.

E. Timetable for Submission of Assessments

Centocor Ortho Biotech Inc will submit REMS Assessments to FDA 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Centocor Ortho Biotech Inc will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix 1 Dear Infusion Center Letter



June 2009

IMPORTANT DRUG WARNING

Dear Infusion Center:

Centocor Ortho Biotech Inc., the makers of REMICADE[®] (infliximab), would like to inform infusion center personnel of important safety information regarding risk of serious fungal infections associated with Tumor Necrosis Factor-alpha (TNF α) blockers.

On 04 September 2008, the U.S. Food and Drug Administration (FDA) issued an Alert on invasive fungal infections reported in association with TNF blockers. The FDA reported histoplasmosis and other invasive fungal infections not consistently recognized in patients taking the Tumor Necrosis Factor- α blockers: REMICADE, Cimzia[®] (certolizumab pegol), Enbrel[®] (etanercept), and Humira[®] (adalimumab).¹ This has resulted in delays in appropriate antifungal treatment, sometimes resulting in death.

REMICADE[®] (infliximab) is indicated for the treatment of adults with rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis and for children with Crohn's disease.

Important information about the risk of invasive fungal infections, such as histoplasmosis, is listed in the *Boxed Warning* and *Warnings* sections of REMICADE's prescribing information and the Medication Guide for patients.

The following should be considered by infusion centers administering REMICADE and by healthcare professionals providing supportive care to patients receiving REMICADE:

- **Please provide and review the Medication Guide with your patients at each infusion and encourage them to discuss any questions with you.**
- TNF blockers are immunosuppressants. Patients receiving TNF blockers, including REMICADE, are at risk for developing infections including invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections.
- Healthcare professionals should be alert to this risk in REMICADE-treated patients, particularly if they reside in or travel to regions endemic for histoplasmosis, coccidioidomycosis, or blastomycosis (eg, Ohio and Mississippi River valleys or the Southwestern United States). Invasive fungal infections should be suspected if they develop a serious systemic illness.
- Patients should be encouraged to report signs of infection and be closely monitored during and after treatment with REMICADE for the development of signs or symptoms of possible systemic fungal infection including fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates on x-ray, or serious systemic illness, including shock.
- Patients who develop an infection, including any persistent or reoccurring infections, should be discontinued from REMICADE therapy and undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, antigen detection and serum antibody titers. Empiric antifungal therapy should be considered until the pathogen(s) are identified and in consultation with an infectious diseases specialist when feasible.
- REMICADE, or other TNF α blocker, may be restarted after recovery from the infection. The decision to restart REMICADE should include a reevaluation of the benefits and risks of TNF blocker therapy, especially in patients who live in regions of endemic mycoses. Both the decision to restart REMICADE and the duration of antifungal therapy should be made in consultation with an infectious diseases specialist, when feasible.

For further information please refer to the following FDA links:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124185.htm>

<http://www.accessdata.fda.gov/psn/printer.cfm?id=878>

PLEASE NOTE: This letter does not include a comprehensive description of the serious and significant risks associated with the use of REMICADE. Please read the accompanying full prescribing information and Medication Guide for a complete description of the serious and significant risks associated with the use of REMICADE, including Boxed Warning regarding the risk of serious infections, Contraindications, Warnings, Precautions, and Adverse Events.

Healthcare professionals and infusion center personnel should report cases of serious fungal infections or any serious adverse events suspected to be associated with the use of REMICADE to Centocor Ortho Biotech Services, LLC Medical Affairs Department at 1-800-457-6399.

Alternatively, this information may be reported to FDA's MedWatch reporting system by:

- phone (1-800-FDA-1088)
- facsimile (1-800-FDA-0178)
- the MedWatch website at <http://www.fda.gov/medwatch>
- or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Healthcare professionals, infusion center personnel and consumers should use Form 3500 for reporting adverse events.

Each vial of REMICADE is accompanied by the full prescribing information, which includes the Medication Guide. The box for each single vial also contains the following instructions: "Provide Medication Guide to Patient." Additional copies of the Medication Guide are available for download on www.remicade.com.

We ask that you disseminate this letter to the healthcare professionals within your center through your standard communication methods. Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor Ortho Biotech Services, LLC Medical Affairs Department at 1-800-457-6399. We appreciate your collaboration with communicating this important information.

Sincerely,

Peter Callegari, MD
Vice President, Medical Group
Immunology Medical Affairs
Centocor Ortho Biotech Services, LLC

References:

Information for Healthcare Professional REMICADE (infliximab), Cimzia[®] (certolizumab pegol), Enbrel[®] (etanercept), and Humira[®] (adalimumab).
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124185.htm>. Accessed 16 June 2009.

Appendix 2 Dear Healthcare Provider Letter



June 2009

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor Ortho Biotech Inc., the makers of REMICADE[®] (infliximab), would like to inform you of important safety information regarding risk of serious fungal infections associated with Tumor Necrosis Factor-alpha (TNF α) blockers.

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Important information about the risk of invasive fungal infections, such as histoplasmosis, is listed in the *Boxed Warning* and *Warnings* sections of REMICADE's prescribing information and the Medication Guide for patients.

The following should be considered by REMICADE prescribers and by healthcare professionals providing supportive care to patients receiving REMICADE:

- TNF blockers are immunosuppressants. Patients receiving TNF blockers, including REMICADE, are at risk for developing infections including invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections.
- Healthcare professionals should be alert to this risk in REMICADE-treated patients, particularly if they reside in or travel to regions endemic for histoplasmosis, coccidioidomycosis, or blastomycosis (eg, Ohio and Mississippi River valleys or the Southwestern United States). Invasive fungal infections should be suspected if they develop a serious systemic illness.
- Patients should be encouraged to report signs of infection and be closely monitored during and after treatment with REMICADE for the development of signs or symptoms of possible systemic fungal infection including fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates on x-ray, or serious systemic illness, including shock.
- Patients who develop an infection, including any persistent or reoccurring infections, should be discontinued from REMICADE therapy and undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, antigen detection and serum antibody titers. Empiric antifungal therapy should be considered until the pathogen(s) are identified and in consultation with an infectious diseases specialist when feasible.
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Alternatively, this information may be reported to FDA's MedWatch reporting system by:

- phone (1-800-FDA-1088)
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- or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Both healthcare professionals and consumers should use Form 3500 for reporting adverse events.

Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor Ortho Biotech Services, LLC Medical Affairs Department at 1-800-457-6399.

Sincerely,

Peter Callegari, MD
Vice President, Medical Group
Immunology Medical Affairs
Centocor Ortho Biotech Services, LLC

References:

Information for Healthcare Professional REMICADE (infliximab), Cimzia[®] (certolizumab pegol), Enbrel[®] (etanercept), and Humira[®] (adalimumab).
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124185.htm>. Accessed 16 June 2009.

Appendix 3 REMICADE® (infliximab) Serious Fungal Infections Education Guide



REMICADE® (infliximab) Serious Fungal Infection Education Guide

- **Treatment with REMICADE or other anti-TNF α agents puts patients at increased risk for serious infections including invasive fungal infections that can lead to hospitalization and death.**
- **Invasive fungal infections including histoplasmosis and coccidioidomycosis and other opportunistic fungal infections are frequently unrecognized.**
 - Patients being treated with REMICADE or other anti-TNF α agents are more susceptible to invasive fungal infections, especially when residing in, or visiting endemic areas of the world.
- **Invasive fungal infections are frequently unrecognized and treatment is frequently delayed.**
 - If these conditions are not considered in the differential diagnosis, appropriate therapy may be delayed with potentially life-threatening consequences.
 - Patients, including those being treated with REMICADE or other anti-TNF α agents, may present with disseminated infection rather than local disease.
 - Antigen and antibody tests for these invasive fungi may be falsely negative in patients being treated with REMICADE or other anti-TNF α agents. Patients should undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, as well as antigen detection and serum antibody titers.

- Patients have died when the initial physician who came in contact with the patient did not consider or recognize the invasive fungal infection (eg, histoplasmosis, coccidioidomycosis).
 - Invasive fungal infections must always be considered when a patient receiving REMICADE or other anti-TNF α agents presents acutely ill, particularly with a history of residence in or travel to endemic areas. A high index of suspicion is key to appropriate management of this risk.
 - Urgent consultation with an infectious disease specialist and/or empiric antifungal therapy should be considered in patients at risk for invasive fungal infections, including those being treated with REMICADE or other anti-TNF α agents who develop severe systemic illness.

Background: Systemic Fungal Infections

1. Exposure

- a. Result of airborne exposure to organisms that cause histoplasmosis or coccidiomycosis or other fungal agents
- b. Increased in areas endemic for specific fungal agents
 - 1) Histoplasmosis - Ohio and Mississippi River valley (prevalence – up to 80%)
 - 2) Coccidioidomycosis - Southwestern US particularly Arizona and the San Joaquin Valley in California (prevalence – up to 50%)

2. Other Risk Factors

- a. Immunosuppression
- b. Chronic lung disease
- c. Elderly and Children less than 2 years old
- d. Occupation (farmers, construction workers, spelunkers)
- e. Exposure to a large inoculum (ie, dust storms)

3. **The role of tumor necrosis factor-alpha (TNF- α) in severe fungal infections**
 - a. TNF- α may play a role in granuloma formation and containment of fungal infection
 - b. Cases of severe fungal infections including histoplasmosis and coccidioidomycosis have been reported in patients treated with anti-TNF therapies and have resulted in death.
4. **Active Disease**
 - a. Patients should be closely monitored during and after treatment with REMICADE for the development of signs or symptoms of possible systemic fungal infection including fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates on X-ray, or serious systemic illness including shock.
 - b. Patients who develop an infection should be discontinued from REMICADE therapy and undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, antigen detection and serum antibody titers.

Before initiating and during treatment with REMICADE

Manage the potential risk of severe fungal infection with proper evaluation, monitoring and treatment.

1. **Evaluate:** Make a thorough history (including history of residence in or travel to endemic areas), physical, and, if indicated, evaluation (eg, laboratory tests, chest x-ray) part of your regular examination.
2. **Monitor:** Continue to monitor patients for signs and symptoms of systemic fungal infection (eg, respiratory symptoms, a general ill feeling, fever, chest pains, and a dry or nonproductive cough).
3. **Treat:** While diagnostic workup is being performed, appropriate empiric anti-fungal therapy should be considered and/or consultation with an infectious disease specialist for patients with signs and symptoms of systemic fungal infection. Empiric treatment is not a substitute for thorough work-up to establish definitive diagnosis and therapy.